Cancer Causes and Control, 4, 203 - 208

Is breast size a predictor of breast cancer risk or the laterality of the tumor?

Ruby T. Senie, Audrey F. Saftlas, Louise A. Brinton, and Robert N. Hoover

(Received 5 November 1992; accepted in revised form 25 January 1993)

The relationship of breast size both to breast cancer risk and to the laterality of the tumor was studied among 261 women diagnosed with breast cancer and 291 control subjects who were enrolled in the United States' Breast Cancer Detection and Demonstration Project from 1973 to 1980. Standardized measures of breast area were obtained by applying planimetry to bilateral screening mammograms taken four years before breast cancer was diagnosed in case subjects. The left breast was larger in 53 percent of women with breast cancer and in 60 percent of women in the control group; the difference in breast area by laterality was significant only among controls ($P = 0.01$). To assess breast cancer risk, breast area was categorized by quartiles, with the lowest quartile being the referent group. Risk was increased minimally among women with the largest breast area (odds ratios = 0.9, 0.9, 1.2); however, the point estimates were not statistically significant and there was no evidence of a linear trend. Left-sided disease was diagnosed in 51 percent of women in the case group. Although the mean area of the breast with the malignancy did not differ significantly from the opposite breast, cancer developed in the larger breast of 57 percent of women with left- and 46 percent of women with right-sided disease. Breast size was associated with cancer of the left breast but not the right. However, these size differences were small since the area of the larger breast was less than 10 percent greater than the smaller breast among half of the case subjects. Further research is required to identify factors associated with the susceptibility of breast tissue to malignant transformation among women with unilateral disease.

Key words: Breast size, breast cancer risk, tumor laterality, United States.

Introduction

Whether any relationship exists between breast size and breast cancer risk has been questioned.[1-6] One recent study[2] reported an increased risk with increasing breast size; other investigators[3] noted the association was present only among postmenopausal women. Since a strong correlation between body weight and breast size was noted in both studies, the analyses controlled for body mass or weight relative to height. A study[4] in which increasing breast size was associated positively with breast cancer risk only among women with a history of proliferative benign breast disease did not include body mass measurements in the analysis. Two older studies[5,6] did not observe a difference in breast size when breast cancer patients were compared with control subjects. Researchers have used various techniques to quantify differences in breast size among women including comparison of bra cup sizes,[2,3] self-assessments,[4,5] and mammography.[6]

Dr Senie is with Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Authors are also affiliated with the Centers for Disease Control and Prevention (Dr Saftlas), Atlanta, GA and the National Cancer Institute (Drs Brinton and Hoover), Bethesda, MD, USA. Address correspondence to Dr Senie, Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York, 10021, USA.

Anatomy texts[7] have long noted that a woman's breasts are seldom equal in size, with the left breast tending to be slightly larger than the right. In addition, among women diagnosed with unilateral breast cancer, a predominance of left-sided disease has been observed, with the left:right ratio varying from 1.05 to 1.26.[8-10] Some investigators[1c] have hypothesized that greater frequency of left-sided disease may be associated with the greater amount of tissue at risk in the left breast.

To explore the risk of breast cancer and the laterality of malignancy to breast size, we measured prediagnostic mammograms by planimetry to obtain standardized measures of breast area.

Materials and methods

The study subjects were enrolled between 1973 and 1975 in one of 25 of the 29 centers of the Breast Cancer Detection and Demonstration Projects (BCDDP), a United States nationwide breast-cancer screening-program which was sponsored jointly by the American Cancer Society and the US National Cancer Institute.

The case subjects were newly diagnosed with primary breast cancer during their fifth year of participation (1978 through 1980); six women with bilateral breast cancer were excluded. The control subjects, who remained free of breast cancer during the same screening interval, were matched to the women with cancer by screening center, five-year age category, race (White, Black, Asian, or other), date of enrollment in BCDDP (within six months), and duration of screening participation. After exclusions for missing data, 261 case subjects and 291 controls were included in these analyses.

Interviews were conducted at home to collect data on breast cancer risk-factors including demographic and personal characteristics, smoking and drinking, present and past body build, hormone use, past medical and reproductive history, and family history of breast cancer. Details concerning interview procedures were previously published.[11] Measurements taken at the time of first screening were used to calculate body mass index (BMI), *i.e.*, body weight (kg) divided by height (m^2).

Breast area measurements were determined from prediagnostic mammograms taken four years earlier at the time of the first screening exam.[11] A planimeter was applied to the caudal projections to determine total area (cm^2) of each breast.[12] Two methods were used to assess breast size: (i) the area of the left breast was compared with the area of right; and (ii) the area of the larger breast was compared with the area of the smaller breast, regardless of laterality. The percent difference in area was calculated to assess the degree of breast asymmetry. This continuous variable was categorized to: less than 10 percent; 10-19.9 percent; 20-29.9 percent; and 30 percent or greater. Ten women were excluded from these analyses because their calculated breast areas on the first and fourth mammographic films differed by more than 50 percent and were judged to be in error. Among case subjects, the area of the breast in which cancer was diagnosed was compared with the area of the opposite breast.

Case-control comparisons and analyses among case subjects by laterality of malignancy were evaluated by chi-square tests applied to contingency tables. Associations among continuous variables were assessed by calculating Pearson correlation coefficients, paired and Student *t*-test statistics, and analysis of variance. The association between breast cancer risk and breast size was estimated by quartiles of breast area: $< 695\ cm^2$ (referent category); 695-995 cm^2; 996-1,392 cm^2; and $\geq 1{,}393\ cm^2$. Logistic regression analysis was used to obtain adjusted odds ratios (OR) and to investigate the potential effects of interaction and confounding.[13]

Results

Case-control comparisons

Case and control subjects were similar regarding age at entry to screening, race, parity, and BMI (Table 1). The mean age at entry to screening was 53 years (standard deviation = 9.3). The majority of subjects were White (87 percent). Although menopausal status did not differ significantly by case-control status, the proportion of women with surgical menopause was greater among control (37 percent) than case subjects (29 percent). Significantly more case subjects (34 percent) than control subjects (24 percent, $P < 0.01$) reported a family history of breast cancer in a primary (mother or sister) and/or secondary (all others) relative. In addition, more women diagnosed with breast cancer (25 percent) than control subjects (16 percent, $P = 0.01$) reported prior breast surgery. BMI did not differ when cases and controls were compared; subset analyses by menopausal status did not alter these findings.

Although the range of breast area was greater among women with breast cancer than among those without disease, no significant difference in mean area of the larger or smaller breast was observed among women in either group (Table 2). On average, the larger breast was 15 percent greater in area than the smaller breast and the degree of asymmetry was less than 10 percent among a majority of study subjects (51 percent of case subjects and 53 percent of control subjects).

Table 1. Distribution of cases and controls by selected demographic factors, Breast Cancer Detection and Demonstration Project (USA), 1973-80

Variable	% of cases (No. = 261)	% of controls (No. = 291)
Age at entry (yrs)		
< 45	19	21
45-54	33	34
55-64	33	31
≥ 65	15	14
Race		
White	86	87
Black	7	6
Other	7	7
Menopausal status		
Premenopausal	22	20
Natural menopause	47	41
Surgical menopause	29	37
Unknown	2	2
Body mass index[a]		
< 22	28	31
22-23.9	24	22
24-26.9	26	22
≥ 27	22	25
Family history of breast cancer[b]		
None	62	76
Primary relative	26	14
Secondary relative	8	8
Both primary and secondary	4	2
History of breast surgery[b]		
Negative	75	84
Positive	25	16

[a] Body mass index = weight/height^2.
[b] $P < 0.01$.

Breast size by laterality

The area of the left breast was strongly correlated with the right breast ($r = 0.91$) for both groups; however, more women in the control group (60 percent) had a larger left breast than did women with breast cancer (53 percent). Among control subjects, the area of left breast was significantly larger than that of the right ($P = 0.01$); in contrast, a smaller difference in breast area by laterality was noted among cases. After selecting case and control subjects with asymmetry of 10 percent or greater, the left breast was found to be larger in 65 percent regardless of disease status.

Menopausal status was found to be a statistically significant factor; the difference by left:right area was significant only among postmenopausal control subjects. Among these women, parity was associated with the laterality of the larger breast; the left breast was larger than the right in 62 percent of parous women and 51 percent of nulliparous women. However, this difference did not reach statistical significance.

Table 2. Distribution of cases and controls by selected breast-size measurements, Breast Cancer Detection and Demonstration Project (USA), 1973-80

Variable	Cases (No. = 261)	Controls (No. = 291)
Area (cm^2)	*Mean (SD)*	*Mean (SD)*
Larger breast	1,097.6 (521.8)	1,074.4 (508.3)
Smaller breast	972.6 (472.9)	957.2 (475.1)
Right breast	1,026.2 (500.8)	999.0 (483.9)
Left breast	1,044.1 (502.8)	1,032.6 (506.2)
Range of area (cm^2)	166-3,148	238-2,811
Larger breast		
Left	53%	60%
Right	43%	38%
Equal	4%	2%
Degree of asymmetry[a]		
< 10%	51%	53%
10-19%	26%	24%
20-29%	11%	13%
≥ 30%	12%	9%

[a] Degree of asymmetry = $100 - \frac{\text{smaller breast area}}{\text{larger breast area}}$.

Breast size and demographic factors

Correlations of breast area measurements with demographic factors were computed separately for cases and controls. The area of the larger breast was correlated significantly with age at entry to screening, weight, and BMI; however, breast area was not associated with height (Table 3). The strength of the correlation of

Table 3a. Correlation coefficients for the relationship of weight, height, body mass index, and age at entry to screening with area of the larger breast, Breast Cancer Detection and Demonstration Project (USA), 1973-80

Variable	Cases (No. = 259)[a]	Controls (No. = 283)[a]
Weight	0.64[b]	0.61[b]
Height	0.01	0.05
Body Mass Index	0.69[b]	0.67[b]
Age at entry	0.24[b]	0.26[b]

Table 3b. Correlation coefficients for the relationship of body mass index with area of the larger breast by category of age at entry to screening

Age group	Cases (No. = 259)[a]	Controls (No. = 283)[a]
< 45	0.73[b]	0.67[b]
45-54	0.67[b]	0.66[b]
55-64	0.71[b]	0.62[b]
≥ 65	0.59[b]	0.44[b]

[a] Weight and height were not recorded for 2 cases and 8 control subjects.
[b] $P < 0.001$.

breast area with BMI was weaker among women aged 65 years and older than among younger women. Breast area was not associated with number of full-term pregnancies or duration of hormone use for either contraception or menopausal symptoms. Breast size was similar for women with and without a family history of breast cancer.

Prior benign breast surgery was reported by 109 women—64 case subjects and 45 controls. Paired *t*-tests indicated no difference in the area of the left and right breasts and no difference in degree of asymmetry among women with prior breast surgery, regardless of their disease status.

Breast size and breast cancer risk

To assess breast cancer risk, breast area was categorized by quartiles, with the lowest quartile being the referent group. We estimated the crude and adjusted breast cancer ORs (Table 4). Risk did not vary significantly with increasing breast size (crude ORs = 0.9, 0.9, 1.2) and there was no evidence of a linear trend by quartiles of breast area. The odds were not altered significantly after adjusting for age at entry to the screening program, family history of breast cancer, and BMI in the logistic model.

Comparisons by laterality among case subjects

Demographic factors and breast size measurements were assessed by laterality of breast cancer among case subjects (Table 5). Left-breast cancer was diagnosed in 51 percent and right-sided disease in 49 percent. Although paired *t*-test analyses indicated no significant difference in the mean area of the breast in which cancer was diagnosed compared with the area of the opposite breast, cancer developed in the larger breast of 57 percent of women with left-sided and 46 percent of women with right-sided disease. The larger breast was at greater risk only when cancer developed in the left breast ($P < 0.03$). However, the degree of asymmetry was less than 10 percent in approximately half of the cancer patients regardless of tumor laterality.

Age at cancer diagnosis, at menarche, at first birth, or at menopause did not differ when women with left or right breast cancer were compared. In addition, laterality did not differ in relation to BMI, total parity, family history of breast cancer, or a history of exogenous hormone use.

Table 4. Breast cancer odds ratios (OR) associated with breast area, Breast Cancer Detection and Demonstration Project (USA), 1973-80

Breast area (cm^2)	No. of cases	No. of controls	Crude ORs	Adjusted ORs[a]	(CI)[b,c]
< 695	66	75	1.0	1.0	Referent
695-995	62	73	0.9	0.9	(0.5-1.5)
996-1,392	67	79	0.9	0.9	(0.5-1.5)
≥ 1,393	66	64	1.2	1.1	(0.6-2.1)

[a] Adjusted for age at entry, body mass index, and family history of breast cancer.
[b] CI = 95% confidence intervals.
[c] Trend analysis not significant.

Table 5. Laterality of 261 primary breast-cancer cases by selected demographic variables and breast-size measurements, Breast Cancer Detection and Demonstration Project (USA), 1973-80

Variable	Laterality of breast cancer	
	Left (No. = 132)	Right (No. = 129)
Larger breast		
Right	40%	46%
Left	57%	49%
Equal	3%	6%
Area right breast (cm^2)	1,063.8 (520.9)[a]	987.7 (478.2)[a]
Area left breast (cm^2)	1,075.9 (494.9)[a]	1,012.3 (510.8)[a]
Degree of asymmetry (%)		
< 10	54%	48%
10-19.9	26%	26%
20-29.9	11%	12%
≥ 30	10%	14%
Menopausal status		
Premenopausal	22%	22%
Postmenopausal	78%	78%
Parity		
Nulliparous	21%	18%
Parous	79%	82%

[a] Standard deviation.

Discussion

Breast size by laterality

Our results, based on measurements of prediagnostic mammograms by planimetry, confirm the frequently noted breast-size asymmetry with the left breast more often larger than the right.[9] However, the difference by laterality was statistically significant only among control subjects.

Investigators have used a diversity of methods to measure breast size including ultrasound,[14] biosteriometry,[15] water displacement techniques,[16,17] mammograms,[3,12] radiographs,[18] and plaster casting.[19-21] Asymmetry was noted frequently with the left breast often found to be larger.[10,15,16,21] Breast size has been studied in relation to race,[6] functional capacity of the breast at time of lactation,[17] and volume changes during

the menstrual cycle.[14,16] Accurate breast size measurements also are required for symmetric breast reconstruction postmastectomy.[15,21]

Standardized measurements of area enabled us to assess the degree of asymmetry when breasts were not of equal size. Because of variations in positioning and completeness of breast tissue coverage during mammography, we expected some difference in calculated breast area from bilateral mammograms. Interestingly, the area of the larger breast was less than 10 percent greater than the area of the smaller breast among similar proportions of women who developed breast cancer and those who remained healthy.

Using biosteriometric methods, Loughry and colleagues[15] observed a similar proportion (47 percent) of healthy women with breast asymmetry of less than 10 percent. These investigators also noted that the left breast was larger in 13 of 20 women free of benign or malignant breast disease.[22] Several researchers[14,20] have suggested breast volume may vary during the menstrual cycle, while others[19] attribute the variability to measurement techniques. Both factors may have influenced breast size in a study[14] using ultrasound measurements in which volume changes ranged from 16 to 36 percent in premenopausal women.

Case-control comparisons

In our study, there were no significant differences in mean breast area by disease status diagnosed four years after first screening. These results agree with two earlier investigations[5,6] but are in contrast with several recent reports.[2-4]

Our findings agree with a case-control study[5] which relied on self-assessed breast size (small, average, or large). These investigators also observed asymmetry only among controls. Our results are in contrast with two recent studies[2,3] which reported a weak increased risk of breast cancer among postmenopausal women with larger bra cup size. However, their findings may be influenced by the heterogeneity of their study populations in contrast to the BCDDP participants who were primarily Caucasian. The association was positive among Caucasian Hawaiian women but not among Hawaiians of Japanese descent.[2] In a multi-site study,[3] increased risk associated with bra cup size was not significant after controlling for obesity. The elevated risk ratios noted in these studies may have been influenced by differences in the proportion of subjects wearing bras and the comparability of bra sizes across populations.

Our findings also conflict with those of Dupont and Page[4] who observed an increased risk of breast cancer associated with self-assessed larger breast-size among women with proliferative benign conditions and a family history of breast cancer. Inaccurate self-assessment may have led to some misclassification in this study of a relatively small number of cases. Therefore, these findings should be viewed with caution.

Breast cancer risk in relation to breast size was studied after the formula for the volume of a cone was applied to the left mammogram of 42 case-control pairs.[6] Although their findings agree with ours, different methods were used: the films were diagnostic as opposed to screening mammograms, free of detectable cancer, used in our study; and volume rather than area was calculated. However, these investigators provided an estimate of the validity of measuring breast size from mammography by comparing calculated volume with actual volume of 15 excised breasts; the correlation coefficient of the two measurements was 0.975.[6]

Laterality among women with breast cancer

Among our case subjects, the predominance of left-sided breast cancer was small; however, our results indicated that laterality of breast cancer is not associated with breast size measured before the detection of malignancy. This finding conflicts with the hypothesis of several investigators,[10] who suggested larger breast size may be associated with greater frequency of left-sided breast cancer. Others[23] have suggested that genetic differences may influence both breast size and breast cancer laterality. Our results indicate no relationship between family history of breast cancer and area of the larger breast. We also found no association between breast area and breast cancer risk after controlling for family history status.

An alternative hypothesis for the observed left:right ratio is a potential difference in sensitivity of breast tissue to hormonal stimulation. Asymmetry has been recognized as a natural phenomenon[24] and has been induced artificially by unilateral applications of estrogenic preparations to the skin of the human breast.[25] Other investigators[26] have suggested that the predominance of left-sided disease may be associated with easier detection of a tumor in the left breast by right-handed women. Our study supports this hypothesis since we did not find a significant excess of left-sided breast cancer among our cases who were enrolled in a breast cancer screening program enhancing detection of non-palpable tumors.

Because breast cancer develops only in glandular tissue, the relationship between total volume and glandular tissue is an important consideration. In a necropsy study,[18] radiographs of serially sectioned mastectomy-specimens were measured to compare glandular with total volume of the left breasts of Japanese women.

Although a decrease in total breast-volume with increasing age was observed, the volume of glandular tissue remained constant. Therefore, the ability to assess breast cancer risk related to breast size more accurately may rely on studies using magnetic resonance imaging[27] or other noninvasive techniques.

Conclusions

We found no significant differences in breast area four years before diagnosis among women who developed breast cancer and women who remained free of disease. Our findings, however, do confirm the presence of breast asymmetry with a greater proportion of women having larger left breasts. Furthermore, among case subjects, the larger breast was at greater risk of cancer only when the disease occurred in the left breast. Future research may identify factors associated with susceptibility of breast tissue to malignant transformation among women with unilateral breast cancer.

References

1. Catchpole BN. Breast size and cancer [Letter]. *Br Med J* 1977; **i:** 776.
2. Kolonel LN, Nomura AM, Lee J, Hirohata T. Anthropometric indicators of breast cancer risk in postmenopausal women in Hawaii. *Nutrition & Cancer* 1986; **8:** 247-56.
3. Hsieh CC, Trichopoulos D. Breast size, handedness and breast cancer risk. *Eur J Cancer* 1991; **27:** 131-5.
4. Dupont WD, Page DL. Breast cancer risk associated with proliferative disease, age at first birth and a family history of breast cancer. *Am J Epidemiol* 1987; **125:** 769-79.
5. Wynder EL, Bross IJ, Hirayama T. A study of the epidemiology of cancer of the breast. *Cancer* 1960; **13:** 559-601.
6. Katariya RN, Forrest APM, Gravelle IH. Breast volumes in cancer of the breast. *Br J Cancer* 1974; **29:** 270-3.
7. Schaffer JP. *Morris' Human Anatomy.* Philadelphia, PA: Blakiston, 1953: 80-7.
8. Busk T, Clemmesen J. The frequencies of left- and right-sided breast cancer. *Br J Cancer* 1947; **1:** 345-51.
9. Garfinkel L, Craig L, Seidman H. An appraisal of left and right breast cancer. *JNCI* 1959; **23:** 617-31.
10. Senie RT, Rosen PP, Lesser ML, Snyder RE, Schottenfeld D, Duthie K. Epidemiology of breast carcinoma. II. Factors related to the predominance of left-sided disease. *Cancer* 1980; **46:** 1705-13.
11. Saftlas AF, Hoover RN, Brinton LA, Szklo M, Olson DR, Wolfe JN. Mammographic densities as indicators of breast cancer risk. *Cancer* 1991; **67:** 2833-8.
12. Wolfe JN, Saftlas AF, Salane M. Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case-control study. *Am J Radiol* 1987; **148:** 1087-92.
13. *BMDP Statistical Software.* Los Angeles, CA: BMDP, 1991.
14. Malini S, Smith EO, Goldzieher JW. Measurement of breast volume by ultrasound during menstrual cycles and with oral contraceptive use. *Obstet Gynecol* 1985; **66:** 538-41.
15. Loughry CW, Sheffer DB, Price TE, *et al.* Breast volume measurement of 598 women using biosteriometric analysis. *Ann Plast Surg* 1989; **22:** 380-5.
16. Milligan D, Drife JO, Short RV. Changes in breast volume during normal menstrual cycle and after oral contraceptives. *Br Med J* 1975; **11:** 494-6.
17. Hytten FE. Clinical and chemical studies in human lactation: the functional capacity of the breast. *Br Med J* 1954; **1:** 912-5.
18. Sasano N, Tateno H, Stemmermann GN. Volume and hyperplastic lesions of breasts of Japanese women in Hawaii and Japan. *Prev Med* 1978; **7:** 196-204.
19. Campaigne BN, Katch VL, Freedson P, Sady S, Katch FI. Measurement of breast volume in females: description of a reliable method. *Ann Hum Biol* 1979; **6:** 363-7.
20. Nassar AM, Smith RE. Menstrual variations in thermal properties of the human breast. *J Appl Physiol* 1975; **39:** 806-11.
21. Smith DJ, Palin WE, Katch VL, Bennett JE. Breast volume and anthropometric measurements: normal values. *Plast Reconstr Surg* 1986; **78:** 331-5.
22. Loughry CW, Sheffer DB, Price TE Jr, *et al.* Right and left volume and volume distribution comparisons in normal and tumor-containing breasts. *Cancer Det Prev* 1987; **10:** 215-21.
23. McManus IC. Predominance of left-sided breast tumors [Letter]. *Lancet* 1977; **ii:** 297-8.
24. Geschickter C. *Diseases of the Breast, 2nd Ed.* Philadelphia, PA: Lippincott, 1945: 111-19.
25. MacBryde CM. The production of breast growth in the human female. *JAMA* 1939; **112:** 1045-9.
26. Hartveit F. The side and size of breast tumours. *Clin Oncol* 1983; **9:** 135-42.
27. Fowler PA, Casey CE, Cameron GG, Foster MA, Knight CH. Cyclic changes in composition and volume of the breast during the menstrual cycle, measured by magnetic resonance imaging. *Br J Obstet Gynecol* 1990; **97:** 595-602.